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RADIATION THERAPY FOR METASTATIC BRAIN TUMORS FROM LUNG CANCER

A REVIEW TO DEVISE INDIVIDUALIZED TREATMENT PLANS

YOSHIYUKI ITOH, NOBUKAZU FUWA and KOZO MORITA

Department of Radiation Oncology,
Aichi Cancer Center Hospital, Nagoya, Japan

ABSTRACT

We retrospectively analyzed patients with brain metastasis from lung cancer to evaluate treatment modalities for metastatic brain tumors and to devise criteria for individualized treatment plans. Between October, 1986 and December, 1994, 90 patients were selected for this study. The majority (67.8%) received whole-brain radiotherapy (WBRT) alone. WBRT following surgical removal was carried out on 14 patients (15.5%). The median dose of radiation therapy was 43.3 Gy for WBRT. The results were as follows: (1) PS (1 and 2 vs. 3 and 4), which showed a significant difference ($p<0.0001$) in survival by both univariate analysis and multivariate analysis, (2) brain metastasis alone or concurrent metastases to other sites ($p=0.0001$) by univariate analysis, (3) the primary lesion controlled or uncontrolled ($p=0.0006$) by univariate analysis, (4) solitary brain metastasis or multiple brain metastases ($p=0.0145$) by univariate analysis. Patients were classified into 3 groups, A (PS1, 2, the primary lesion controlled, no distant metastasis and solitary brain metastasis), B (others except for groups A and C), and C (PS 3,4) based on 4 significant factors. The 1-year survival rates and median survival times were, respectively 75% and 1,767 days in Group A, 40.6% and 313 days in Group B, and 7.8% and 121 days in Group C ($p<0.0001$). Although the possibility of individualized treatment was suggested, based on 4 factors associated with the patient's condition and disease progression before treatment for brain metastasis, further evaluation by randomized clinical trials is needed.

Key Words: Metastatic brain tumor, Lung cancer, Radiation, Prognostic factors

INTRODUCTION

The incidence of lung cancer has shown an increasing trend in recent years and is currently a leading cause of death in male cancer patients in Japan. Aggressive treatment by surgery or recent chemo-radiotherapy for primary lesions in the lung has improved therapeutic outcomes. Lung cancers are the most frequent primary lesions of metastatic brain tumors.[1,2] Considering the rising incidence of patients with lung cancer, the importance of radiation therapy for brain metastases is likely to become increasingly recognized in the future.

It has generally been accepted that many cases of brain metastases from lung cancer are indications for palliative treatment.[3-5] In terms of achieving improvements in neurological

Address correspondence to: Address to: Dr. Yoshiyuki Itoh, Department of Radiology,
Nagoya University School of Medicine
65 Tsuruma-cho Showa-ku, Nagoya 466-8550, Japan
Tel.: +81-52-741-2327 Fax.: +81-52-741-2335

symptoms, whole brain radiotherapy (WBRT)[2,3] has become the main standard treatment, while surgical resection has been performed only in a very limited number of patients.[6)]

Recently, advances in diagnostic imaging[12)] such as CT and MRI have made it possible to detect even a tiny or solitary lesion at the very early stage prior to the appearance of neurological signs. Furthermore, the treatment of brain metastases has been diversified thanks to new developments in surgical techniques[8-11)] and stereotactic radiosurgery[12-15)] represented by the gamma-ray knife. Such developments suggest the need to restructure the therapeutic paradigm from one of uniformly palliative treatment for all to one in which consideration is given to the patient's individual physical and disease status.

In the present clinical study, we retrospectively analyzed patients with brain metastasis from lung cancer to evaluate treatment modalities for resultant brain tumors, and to devise criteria for individualized treatment plans.

MATERIALS AND METHODS

Ninety-seven patients underwent radiation therapy in the Department of Radiation Oncology at Aichi Cancer Center Hospital for metastatic brain tumors arising from lung cancer between October, 1986 and December, 1994. Among these, 90 patients were selected for this study, and 3 with meningeal dissemination and 4 for whom radiation therapy was discontinued after 20 Gy or less of external irradiation were excluded. Table 1 shows the participating patient characteristics: male-to-female ratio, age, performance status (PS: Eastern Cooperative Oncology Group scale), histology, treatment of the primary lesion, presence or absence of primary lesion control, and the number, size, and site of brain metastasis. Informed consent was obtained from all patients. When the onset of the primary lesion in the lung and that of brain metastasis were simultaneous, all primary lesions were treated with radiation alone or combined with chemotherapy. In this instance, the primary lesion was initially treated when no clinical symptoms in the brain were evident, while the metastatic lesion in the brain was treated either during the treatment of the primary lesion or soon thereafter. All patients received steroids to diminish cerebral edema according to each one's individual symptoms.

Table 2 illustrates the methods and dosages of radiation therapy. Some patients with brain metastasis underwent surgical removal but the majority (67.8%) received WBRT alone. WBRT following surgical removal was carried out on 14 patients (15.5%). Twelve patients (13.3%) received local irradiation alone. The WBRT group was initially treated by 6MV X-ray, 5 times a week with 1.0 Gy per fraction which was gradually increased to 1.8 or 2.0 Gy per fraction to avoid brain edema. For patients receiving focal radiation alone, two orthogonal port irradiations, a tangential field irradiation or conformation therapy were performed, although this based on somewhat varied the site and size of the lesion. As for focal radiation administered as a boost following WBRT, two orthogonal port irradiations or a conformation irradiation were carried out. The median dose of radiation therapy was 43.3 Gy for WBRT alone, 44.4 Gy for focal radiation alone, and 55.5 Gy for focal radiation following WBRT.

The primary effects were assessed based on CT or MRI findings after about 4 weeks following treatment. Among patients who had undergone surgical removal, those who did not demonstrate any apparent residual lesion on diagnostic imaging following treatment were evaluated as showing a complete response (CR). For a single metastatic lesion in the brain, a greater than 50% reduction in the area of the lesion observed by CT and/or MRI after treatment was regarded as a partial response (PR). For 2 or more metastatic lesions, judgment was similarly made using the largest lesion. A reduction rate of less than 50% in the area of the lesions was regarded as no change (NC). Patients in whom the area of lesions was larger after treatment than before or in whom new lesions occurred in the brain were regarded as having progressive disease (PD). If an increase in the area of lesions or an occurrence of new lesions were detected at the follow-up examination, which compared the lesion with CT and/or MRI images at the end of treatment, the disease regarded as uncontrolled, otherwise, it was deemed to be controlled. When neurological symptoms occurred or were aggravated, the brain was immediately examined, and if the above control conditions were not satisfied, it was regarded as uncontrolled.

Table 1 Patient characteristics

Male/female	67/23
Median age (yrs)	57
Range (yrs)	33–78
Performance status (ECOG)	
1–2	61 (68%)
3–4	29 (32%)
Histologic type	
adenocarcinoma	56 (62%)
sqamous cell ca.	12 (13%)
small-cell ca.	13 (14%)
large-cell ca.	8 (9%)
unknown	1 (1%)
Onset	
Metachronous	56 (62%)
Synchronous	34 (38%)
Treatment of primary lesion	
operation	36 (40%)
radiation +/– chemotherapy	54 (60%)
Priamry lesion	
controlled	20 (22%)
uncontrolled	70 (78%)
Brain metastases	
alone	21 (23%)
with other metastases	69 (77%)
Number of lesions	
one	29 (32%)
two	17 (19%)
more than two	44 (49%)
Size of brain metastases	
Median (cm)	2.1
Range (cm)	1.0–4.5
Location of brain metastases	
supratentorial alone	61 (68%)
infratentorial alone	4 (4%)
supratentorial and infratentorial	25 (28%)

Table 2 Radiotherapy

Treatment methods	Total radiotherapy doses	
Whole-brain irradiation	61 (67.8%)	
median (Gy)		43.3
(range)		26.4–46.0
Operation and whole brain	14 (15.5%)	
median (Gy)		40.8
(range)		27.6–45.5
Focal irradiation	12 (13.3%)	
median (Gy)		44.4
(range)		33.3–46.6
Whole brain and focal	3 (3.3%)	
median (Gy)		55.5
(range)		51.6–55.5

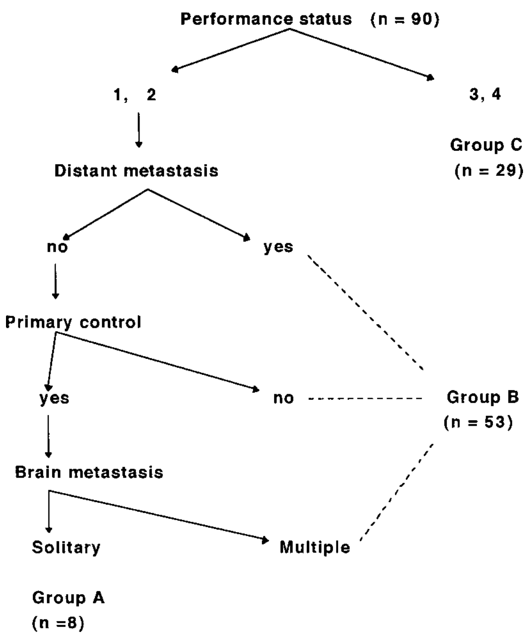

Fig. 1 Division tree of 3 groups by pre-treatment status: A; favorable prognoses, B; intermediate group, C; poor prognoses

It was previously reported that prognostic factors such as PS condition, control of the primary lesion, and extracranial metastasis showed a particularly high correlation with the survival rate in a study of 1,200 patients who underwent RTOG trials[2)] and in other similar studies.[5,11,14)] For cases of a single metastatic lesion in the brain, surgical treatment is becoming more common, although it is relatively still infrequent, and its appropriateness remains controversial. This has been shown not only by retrospective studies but also in randomized clinical trials (RCT), and the importance of surgical treatment for brain metastasis and postoperative WBRT has been debated. As shown in Fig. 1 in the present study, the 90 patients were classified into three groups, namely favorable prognosis group (group A), poor prognosis group (group C) and intermediate group (group B) according to PS, distant metastasis, control of the primary lesion in the lung before treatment for brain metastasis, and the number of brain metastases, the prognosis of each group was then evaluated.

For the calculation of survival times, the day when radiation therapy for brain metastasis was initiated was regarded as the day of treatment. The survival rate was analyzed by the Kaplan-Meier method, and log-rank tests were used for a univariate analysis of prognostic factors. For multivariate analysis, Cox's regression proportional hazard model was employed. In these statistical analyses, $p<0.05$ was regarded as significant, and the analytical data were calculated using a personal computer (Stat View version 4.5J and Survival Tools version 1.1, Abacus Concepts, Berkeley, CA, USA).

RESULTS

The response results for brain metastases were as follows. Overall response rate was 58.8%. CR was observed in 17 patients (18.8%), partial response (PR) in 36 (40.0%), no response (NC) in 26 (28.9%), and progress disease (PD) in 11 (12.2%).

In all 90 patients, the 1-year and 2-year survival rates were 36.7% and 17.8%, respectively, with a median survival period of 233 days (Fig. 2).

Univariate analysis of prognostic factors in 90 subjects was performed by log-rank tests (Table 3). Survival differences were significantly influenced by following 11 factors: gender, PS, therapy for the primary lesion, whether or not the primary lesion was controlled, metastasis to

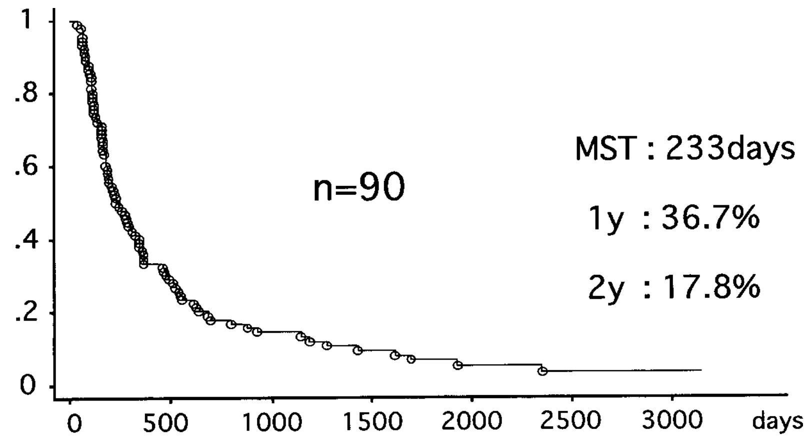

Fig. 2 Survival curve for all cases

Table 3 Univariate analysis by log-rank tests for selected prognostic factors

Covariate	Comparison	p-value
Age (yrs)	< 65 vs. >= 65	0.3156
Sex	Female vs. Male	0.0412
Histology	adenocarcinoma vs. others	0.3095
PS	1,2 vs. 3,4	< 0.0001
Treatment of primary lesion	operation vs. others	0.0011
Primary lesion	controlled vs. uncontrolled	0.0006
Onset	metachronous vs. synchronous	0.193
Brain metastases	alone vs. with other metastases	0.0001
Number of lesions	single vs. multiple	0.0145
Neurologic function	I, II vs. III, IV	0.0109
Headache	none vs. some	0.027
Location	supratentorial vs. infratentorial with/ without supratentorial	0.1245
Total radiation doses	>= 50 Gy vs. < 50 Gy	0.0585
Tumor response	CR, PR vs. NC, PD	0.0048
Chemotherapy	combined vs. not	0.5505
Neurologic function	improved vs. not	< 0.0001

Table 4 Hazard ratio and 95% confidence interval estimated by multivariate analysis including all prognostic factors listed

	Hazard ratio	95%CI	p-value
PS (1, 2 vs. 3, 4)	3.631	2.000–6.592	<0.0001
Extracranial metastases	2.244	0.927–5.431	0.73
Treatment of primary lesion	1.298	0.715–2.357	0.9182
State of primary lesion	0.946	0.328–2.726	0.391
Neurologic function	1.402	0.806–2.439	0.231
Headache	1.332	0.812–2.184	0.2555

CI: confidence interval

sites other than the brain, presence or absence of neurological symptoms (classified by the method described in Reference 3), presence or absence of symptoms of increased intracranial pressure, solitary or multiple brain metastases, treatment modality of the brain lesion, primary effects, and presence or absence of symptom improvements after treatment. Items that showed a significant difference in univariate analysis were evaluated by multivariate analysis. Significant factors were PS, therapy chosen for the primary lesion, control or no control of the primary lesion, metastasis to sites other than the brain, presence or absence of neurological symptoms, and presence or absence of symptoms of increased intracranial pressure (Table 4). Above all, survival significantly depended upon PS alone by multivariate analysis. The most important prognostic factor affecting over all survival was PS.

Patients were classified into 3 groups, A, B and C, as shown in Fig. 1 based on 4 significant factors: (1) PS, which showed a significant difference in survival by both univariate and multivariate analysis ($p<0.0001$), (2) brain metastasis alone or concurrent metastases to other sites ($p=0.0001$ by univariate analysis), (3) primary lesion controlled or uncontrolled ($p=0.0006$ by univariate analysis), (4) solitary brain metastasis or multiple brain metastases ($p=0.0145$ by univariate analysis). Fig. 3 shows the survival curves in the 3 groups. The 1-year survival rate and MST were, respectively, 75% and 1,767 days in Group A (8 cases), 40.6% and 313 days in Group B (53 cases), and 7.8% and 121 days in Group C (29 cases). There were significant differences between groups A and C ($p<0.0001$), and between groups B and C ($p<0.0001$).

With respect to the relationship between the treatment modality for brain metastasis and intracerebral control, the 1-year and 2-year control rates in the brain were, respectively 29.3% and 7.4% in the WBRT alone group, and 64.3% and 40.2% in the surgery and WBRT group. The control rate significantly differed between WBRT alone (61 cases) and surgical removal plus WBRT (14 cases) ($p=0.0248$), and between WBRT alone and WBRT plus focal radiation (3 cases) ($p=0.0296$) (Fig. 4), whereas the Wilcoxon test showed no significant differences between the latter 2 groups.

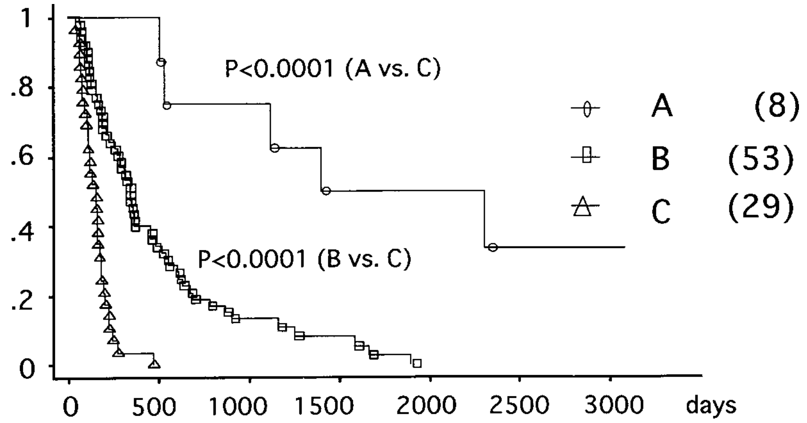

Fig. 3 Survival curves for groups A, B and C

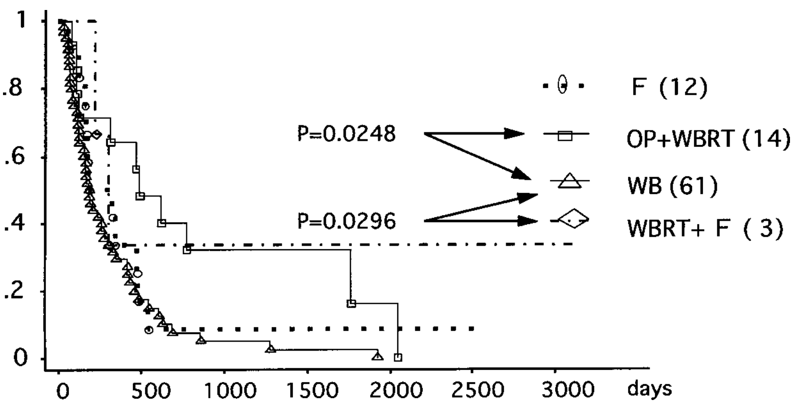

Fig. 4 Intracranial control curves for treatment modality
There is a significant difference between WBRT alone and an operation followed by WBRT, and between WBRT alone and WBRT plus local irradiation.
F, focal radiation; OP + WBRT, operation followed by whole-brain radiotherapy; WBRT, whole-brain radiotherapy; WBRT + F, whole-brain radiotherapy and focal radiation.

Of the 90 patients, 4 survived, 38 died of primary lesions, 23 of systemic metastases, 22 of metastases in the brain, and 3 of other diseases. As for radiation-induced neurotoxicity, since radiation-induced dementia generally occurs at least 6–12 months after radiotherapy, we examined PS, neurological symptoms and systemic conditions at the end of treatment and 2 years after treatment in the 13 patients who had survived for more than 2 years. The above items were recorded in only 7 of those 13 patients. Since the records, of the remaining patients, were insufficient comparisons could not be made. Of the 7 patients, a reduction in PS was observed in 2 due to metastasis in bone and a recurrence of metastatic lesions in the brain, and neurological symptoms were aggravated by the recurrence of metastatic lesions in the brain in 2. As for the remaining 3 patients, their conditions remained unchanged 2 years after treatment. Dementia, which is considered to be a delayed damage induced by irradiation, was not detected in any of the 7 patients.

DISCUSSION

Previous studies have demonstrated poor prognoses in patients who had received radiation therapy for brain metastasis from lung cancer, showing a median survival time of several months.[2,3-5] Although WBRT has been widely carried out in the expectation of alleviating neurological symptoms which may result in improving QOL, it does not have a significant impact on the prognosis.

Recently, however, along with the increasing use of CT and particularly MRI,[7] the diagnostic accuracy for metastatic lesions has been enhanced, and very early small and solitary lesions without neurological symptoms have become apparent.

Consequently, not only aggressive surgical treatment,[8,11] but also RS[12,13] such as that involving the use of a gamma ray knife for metastatic brain tumors have rapidly become prevalent. For a subset of patients with favorable prognoses, even though many patients with brain metastasis from lung cancer usually may still have poor prognoses, it is necessary to devise individualized treatment plans taking account of their general condition and disease progression rather than applying a conventional uniform treatment with WBRT alone. Pre-stratification based on the general condition of the patients and their disease progression before treatment might allow individualized treatment. Since there were no obviously significant differences between Groups A and C, it would be inappropriate to administer the same treatment, at least to these two groups.

In Group A, although the number of patients was limited, a favorable prognosis and an improvement in local control can be expected. Radiation to the brain should be administered taking into consideration the total dose of irradiation and its fraction size to minimize the potential neurotoxicity induced by radiation.[18-20]

Retrospective studies have indicated that the control of metastatic lesions in the brain was higher with WBRT after surgery than with surgery alone.[14,20-22] It was also higher with WBRT after surgery than with WBRT alone.[4] Following radiotherapy performed by RCT, it was reported that both local control and survival rates were improved.[8,9] However, in more recent studies, it was reported that local control was improved by RCT, although it did not improve survival.[14,22]

The reason for the absence of a difference in these findings might have been because most patients died of extracranial disease. Therefore, no consensus has been reached with regard to this question. A further evaluation by RCT is expected using a larger number of patients with similar conditions whose status before entry is accurately known.

In the present study, despite the limitations of a retrospective analysis and the inherent selection bias, there were significant differences in the control of metastatic lesions in the brain among the 3 treatment methods; “OP + WBRT”, “WBRT + F” and “WBRT alone.” However, “WBRT + F” was performed on only 3 patients, the standard treatment during the period being WBRT, and the patients who underwent an excision of metastatic lesions in the brain or “WBRT + F” were specially chosen. There was a strong bias, however, and since these findings alone cannot indicate whether “OP + WBRT” and “WBRT + F” are better than WBRT alone, a comparative examination by RCT will be necessary.

However, in patients showing poor PS such as those in Group C, treatment placing emphasis solely on improvements in neurological symptoms is considered sufficient, and only WBRT should be performed. On the other hand, in patients demonstrating marked improvements in neurological symptoms and favorable tumor size reduction, adding local irradiation, which significantly differs in effect from WBRT alone, is expected to improve their neurological symptoms and to prolong their improved condition. In such cases, additional local treatment by RS may be feasible. First priority should be given to an improvement in QOL. When poor PS is attributable to systemic metastasis, treatment of the brain is less necessary, and conservative measures and supportive care may be sufficient.

This analysis of 90 patients is a review of the cases that had been treated before RS was introduced. Since then RS has already been initiated in our institution.[16] Bindal *et al.*[15] reported that both the recurrence control rate and survival time in the radiosurgery group were inferior to those in the surgery group, whereas other studies[12,13] have suggested that the outcome of radiosurgery compared favorably to that of surgery plus WBRT in cases demonstrating one or two metastatic lesions. Hence, in a group such as Group A, a therapeutic strategy of RS followed by WBRT or reduced-field irradiation may be feasible instead of surgery. In terms of local control, the therapeutic strategy of WBRT plus RS or local irradiation plus RS for inoperable patients or those who refused surgery is fully feasible.

Twelve of 90 patients received irradiation in a localized field instead of WBRT. There was no significant difference in the intracranial control rate between WBRT alone and focal radiation alone. This finding may suggest that solitary lesions or comparatively localized multiple lesions appear to be sufficiently treated by focal radiation alone for patients in Group C; those in Group B whose primary lesion are not controlled; or those in whom distant metastasis and neurological symptoms are already present and for whom symptom relief is expected to improve QOL.

Since Group B (the intermediate group) accounted for the highest percentage of all patients, characterization of this group would be the most valuable. Bindal *et al.*[23] reported that in patients without distant metastasis, whose primary lesions in the lungs are controlled, when all brain metastatic lesions can be surgically removed even including cases of multiple metastases, an improvement in prognosis can be expected to an extent similar to that in patients with solitary lesions who have been totally resected. Therefore, it is suggested that prognoses can be improved by surgical removal of all metastatic lesions or RS in addition to surgery including some lesions that cannot be treated by surgery due to anatomical problems. Even some patients in Group B showed favorable prognoses similar to those in Group A.

In contrast, in Group B, patients with distant metastasis or those showing uncontrolled primary lesions may develop new hematogenous metastases even if WBRT alone or WBRT plus focal radiation could control the brain lesions. Therefore, excluding patients showing multiple metastatic lesions throughout the brain, for those cases showing one or two localized lesions, focal radiation appears to be feasible instead of WBRT, to avoid the risk of late metastasis following radiation.

In conclusion, if patients are classified according to the 4 factors of PS before treatment, metastasis in the brain alone, control of the primary lesion, and a single metastasis in the brain, and if the treatment method is determined according to this classification, such patients would have different prognoses, which suggests the possibility of individualized treatment. However, further evaluation by RCT using a larger number of patients with similar conditions whose status before entry is accurately known is needed to assess the survival and quality of life of the 3 groups.

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